

Message

From: Lobdell, Danelle [Lobdell.Danelle@epa.gov]
Sent: 8/20/2015 8:38:10 PM
To: Rowland, Jess [Rowland.Jess@epa.gov]
Subject: RE: Glyphosate CARC document
Attachments: GLYPHOSATE_Summ Table_Epi Cancer Studies.xlsx; Cancer Epidemiology Summary8_20_2015.docx

Hi Jess,

Attached is the epi cancer summary and the updated cancer literature spreadsheet (includes 3 studies from the IARC that were not used in the Tier II). I adapted the Tier II report for this cancer review purposes. Not sure how to reference the Tier II report or if I can (see my comment in the summary document). I will be back in town August 31st.

Danelle

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National Health and Environmental Effects Research Laboratory
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From: Rowland, Jess
Sent: Thursday, August 20, 2015 9:53 AM
To: Lobdell, Danelle
Subject: RE: Glyphosate CARC document

I will call you

JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

From: Lobdell, Danelle
Sent: Thursday, August 20, 2015 9:52 AM
To: Rowland, Jess
Subject: RE: Glyphosate CARC document

Hi Jess,

Yes, 10:30 works for me. Do you want to call me or should I call you?

Danelle

Danelle T. Lobdell, Ph.D., M.S.
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From: Rowland, Jess

Sent: Thursday, August 20, 2015 9:42 AM

To: Lobdell, Danelle

Subject: Glyphosate CARC document

Importance: High

Hi Danelle

Here is the outline for the Epi section of the CARC document.

I have put in some text to lead into your assessment.

I am free from 10:30 to 11:00 am. Is this a suitable time for us to discuss...

Thanks

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

C. Conclusion

JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

Cancer Epidemiology Summary (Adapted from Glyphosate Tier II Memorandum and consideration of the IARC Glyphosate Monograph)

This cancer epidemiology summary utilizes the literature review conducted by HED in the preparation of the Tier II Review that was conducted in February of 2014 for glyphosate. See this memorandum for information on the methods used for the literature review. Four additional studies were added to this summary that were included in the International Agency for Research on Cancer (IARC) Monograph on Glyphosate (2015).

Ex. 5 Deliberative Process (DP)

Cancer Epidemiology Results

An effect estimate of the relation between glyphosate and other pesticide exposure and several different anatomical cancer sites is included in this literature review. Mainly performed within the AHS cohort, this literature review includes studies of prostate, lung, and colorectal cancer in addition to less common cancers in the human population such as pancreatic and stomach cancer in association with pesticide use. The role of pesticide use and lymphohematopoietic cancers and particularly non Hodgkin lymphoma (NHL) has been studied in several investigations external to the AHS cohort. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available; however, for NHL and other non-solid tumors, several investigations are published. In this section, we present a summary of the studies evaluating the carcinogenic potential of glyphosate and other pesticides in the human population.

Solid Tumor Cancer Studies (non-lymphohematopoietic (LHP) cancers)

Within the AHS study cohort, authors evaluated several anatomical cancer sites in relation to pesticide use. None of these investigations reported a significant statistical association with lifetime use of glyphosate specifically. While these are all initial, hypothesis-generating studies and require further follow-up studies to determine whether the true association with glyphosate is indeed null, the large sample size, extensive exposure data collection and validation, and comprehensive confounding variable adjustment in the AHS supports a conclusion of no association between glyphosate use and solid tumor cancers studied at this time. In a cohort analysis of all glyphosate users, authors did not observe an association with all cancers combined (OR 1.0 (95% CI (0.90, 1.2)) or specific anatomical cancer sites, with the exception of a non-statistically significantly elevated risk of multiple myeloma based upon a small number of glyphosate exposed cases [ADDIN EN.CITE <EndNote><Cite><Author>De Roos</Author><Year>2005</Year><IDText>Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study</IDText><DisplayText>(De Roos et al., 2005)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2005</year></dates><keywords></keywords><isbn>0091-6765

(Print)0091-6765</isbn><custom2>Pmc1253709</custom2><titles><title>Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><pages>49-54</pages><number>1</number><contributors><authors><author>De Roos, A. J.</author><author>Blair, A.</author><author>Rusiecki, J. A.</author><author>Hoppin, J. A.</author><author>Svec, M.</author><author>Dosemeci, M.</author><author>Sandler, D. P.</author><author>Alavanja, M. C.</author></authors></contributors><edition>2005/01/01</edition><language>eng</language><added-date format="utc">1384293793</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Program in Epidemiology, Fred Hutchinson Cancer Research Center and the Department of Epidemiology, University of Washington, Seattle, Washington 98109, USA. deroos@u.washington.edu</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>5644</rec-number><last-updated-date format="utc">1384349385</last-updated-date><accession-num>15626647</accession-num><volume>113</volume></record></Cite></EndNote>]. A discussion of studies external to the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in section under Non-Solid Tumor Sites.

Several AHS nested case-control analyses also provide information concerning the carcinogenic potential of glyphosate; there is no statistical evidence of an association with glyphosate presented across these investigations. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and breast cancer (OR 0.9 (95% CI (0.1, 1.1)) [ADDIN EN.CITE

<EndNote><Cite><Author>Engel</Author><Year>2005</Year><IDText>Pesticide use and breast cancer risk among farmers' wives in the agricultural health study.</IDText><DisplayText>(Engel et al., 2005)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2005</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/15632262</url></related-urls></urls><isbn>0002-9262</isbn><titles><title>Pesticide use and breast cancer risk among farmers' wives in the agricultural health study.</title><secondary-title>Am J Epidemiol</secondary-title></titles><pages>121-35</pages><number>2</number><contributors><authors><author>Engel, L. S.</author><author>Hill, D. A.</author><author>Hoppin, J. A.</author><author>Lubin, J. H.</author><author>Lynch, C. F.</author><author>Pierce, J.</author><author>Samanic, C.</author><author>Sandler, D. P.</author><author>Blair, A.</author><author>Alavanja, M. C.</author></authors></contributors><language>eng</language><added-date format="utc">1290464679</added-date><ref-type name="Journal Article">17</ref-

type><auth-address>Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. engell@mskcc.org</auth-address><rec-number>988</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>15632262</accession-num><electronic-resource-num>161/2/121 [pii]
10.1093/aje/kwi022</electronic-resource-num><volume>161</volume></record></Cite></EndNote>], colorectal cancer (OR 1.6 (95% CI (0.9, 2.9)) [ADDIN EN.CITE

<EndNote><Cite><Author>Lee</Author><Year>2007</Year><IDText>Pesticide use and colorectal cancer risk in the Agricultural Health Study</IDText><DisplayText>(W. J. Lee et al., 2007)</DisplayText><record><dates><pub-dates><date>Jul</date></pub-dates><year>2007</year></dates><urls><related-urls><url><Go to ISI>;/000247155000015</url></related-urls></urls><titles><title>Pesticide use and colorectal cancer risk in the Agricultural Health Study</title><secondary-title>International Journal of Cancer</secondary-title></titles><pages>339-346</pages><number>2</number><contributors><authors><author>Lee, W. J.</author><author>Sandler, D. P.</author><author>Blair, A.</author><author>Samanic, C.</author><author>Cross, A. J.</author><author>Alavanja, M. C. R.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>66</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>ISI:000247155000015</accession-num><electronic-resource-num>10.1002/ijc.22635</electronic-resource-num><volume>121</volume></record></Cite></EndNote>], lung cancer (no results shown due to lack of statistically significant risk estimate) [ADDIN EN.CITE

<EndNote><Cite><Author>Alavanja</Author><Year>2004</Year><IDText>Pesticides and lung cancer risk in the agricultural health study cohort.</IDText><DisplayText>(Alavanja et al., 2004)</DisplayText><record><dates><pub-dates><date>Nov</date></pub-dates><year>2004</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/15496540</url></related-urls></urls><isbn>0002-9262</isbn><titles><title>Pesticides and lung cancer risk in the agricultural health study cohort.</title><secondary-title>Am J Epidemiol</secondary-title></titles><pages>876-85</pages><number>9</number><contributors><authors><author>Alavanja, M. C.</author><author>Dosemeci, M.</author><author>Samanic, C.</author><author>Lubin, J.</author><author>Lynch, C. F.</author><author>Knott, C.</author><author>Barker, J.</author><author>Hoppin, J. A.</author><author>Sandler, D. P.</author><author>Coble, J.</author><author>Thomas, K.</author><author>Blair, A.</author></authors></contributors><language>eng</language><added-date

format="utc">1290464577</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD 20892, USA. alavanjm@mail.nih.gov</auth-address><rec-number>987</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>15496540</accession-num><electronic-resource-num>160/9/876 [pii]
10.1093/aje/kwh290</electronic-resource-num><volume>160</volume></record></Cite></EndNote>], pancreatic cancer (OR (95% CI) 1.1 (0.6, 1.7)) [ADDIN EN.CITE <EndNote><Cite><Author>Andreotti</Author><Year>2009</Year><IDText>Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort.</IDText><DisplayText>(Andreotti et al., 2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/19142867</url></related-urls></urls><isbn>1097-0215</isbn><custom2>PMC2674312</custom2><titles><title>Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort.</title><secondary-title>Int J Cancer</secondary-title></titles><pages>2495-500</pages><number>10</number><contributors><authors><author>Andreotti, G.</author><author>Freeman, L. E.</author><author>Hou, L.</author><author>Coble, J.</author><author>Rusiecki, J.</author><author>Hoppin, J. A.</author><author>Silverman, D. T.</author><author>Alavanja, M. C.</author></authors></contributors><language>eng</language><added-date format="utc">1290464888</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA. andreotg@mail.nih.gov</auth-address><rec-number>990</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>19142867</accession-num><electronic-resource-num>10.1002/ijc.24185</electronic-resource-num><volume>124</volume></record></Cite></EndNote>], and prostate cancer (no results shown due to lack of statistically significant risk estimate) [ADDIN EN.CITE ADDIN EN.CITE.DATA], as well as cutaneous melanoma (no results shown due to lack of statistically significant risk estimate) [ADDIN EN.CITE <EndNote><Cite><Author>Dennis</Author><Year>2010</Year><IDText>Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural health study.</IDText><DisplayText>(Dennis, Lynch, Sandler, & Alavanja, 2010)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2010</year></dates><keywords></keywords><urls><related-

urls<url>http://www.ncbi.nlm.nih.gov/pubmed/20164001</url></related-
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 melanoma in pesticide applicators in the agricultural health study.</title><secondary-
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 7</pages><number>6</number><contributors><authors><author>Dennis, L.
 K.</author><author>Lynch, C. F.</author><author>Sandler, D. P.</author><author>Alavanja,
 M. C.</author></authors></contributors><language>eng</language><added-date
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 num><electronic-resource-num>10.1289/ehp.0901518</electronic-resource-
 num><volume>118</volume></record></Cite></EndNote>]. In a population-based study
 external to the AHS, Canadian researchers reported non-significantly elevated odds of prostate
 cancer in relation to glyphosate use (OR 1.36 (95% CI 0.83, 2.25)) [ADDIN EN.CITE
 <EndNote><Cite><Author>Band</Author><Year>2011</Year><IDText>Prostate cancer risk and
 exposure to pesticides in British Columbia farmers</IDText><DisplayText>(Band et al.,
 2011)</DisplayText><record><dates><pub-dates><date>Feb 1</date></pub-
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 farmers</title><secondary-title>Prostate</secondary-title><alt-title>The Prostate</alt-
 title></titles><pages>168-
 83</pages><number>2</number><contributors><authors><author>Band, P.
 R.</author><author>Abanto, Z.</author><author>Bert, J.</author><author>Lang,
 B.</author><author>Fang, R.</author><author>Gallagher, R. P.</author><author>Le, N.
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 num><electronic-resource-num>10.1002/pros.21232</electronic-resource-
 num><volume>71</volume></record></Cite></EndNote>]. This study enrolled prostate cancer
 cases between 1983-1990, prior to the PSA-era; therefore, the study includes more advanced
 tumors upon diagnosis, and is not comparable to Alavanja et al. (2003), which reflects cases
 during the PSA-era in which cases are typically identified at an earlier stage in the natural
 history of disease. Notably, in a prostate cancer follow-up study within the AHS, Koutros et al.

(2013) did not identify an association with advanced prostate cancer (OR (95% CI) 0.93 (0.73, 1.18)) [ADDIN EN.CITE

<EndNote><Cite><Author>Koutros</Author><Year>2013</Year><IDText>Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study</IDText><DisplayText>(Koutros et al., 2013)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2013</year></dates><keywords></keywords><urls><related-urls><url><http://www.ncbi.nlm.nih.gov/pubmed/23171882></url></related-urls></urls><isbn>1476-6256</isbn><custom2>PMC3590039</custom2><titles><title>Risk of total and aggressive prostate cancer and pesticide use in the Agricultural Health Study</title><secondary-title>Am J Epidemiol</secondary-title></titles><pages>59-74</pages><number>1</number><contributors><authors><author>Koutros, S.</author><author>Beane Freeman, L. E.</author><author>Lubin, J. H.</author><author>Heltse, S. L.</author><author>Andreotti, G.</author><author>Barry, K. H.</author><author>DellaValle, C. T.</author><author>Hoppin, J. A.</author><author>Sandler, D. P.</author><author>Lynch, C. F.</author><author>Blair, A.</author><author>Alavanja, M. C.</author></authors></contributors><language>eng</language><added-date format="utc">1374608917</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, EPS 8115, MSC 7240, Rockville, MD 20852, USA. KoutrosS@mail.nih.gov</auth-address><rec-number>5525</rec-number><last-updated-date format="utc">1374608917</last-updated-date><accession-num>23171882</accession-num><electronic-resource-num>10.1093/aje/kws225</electronic-resource-num><volume>177</volume></record></Cite></EndNote>]. AHS investigators also examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with glyphosate use (maternal exposure to glyphosate: OR (95% CI) 0.61 (0.32, 1.16)); paternal exposure to glyphosate: OR (95% CI) 0.84 (0.35, 2.54)) [ADDIN EN.CITE <EndNote><Cite><Author>Flower</Author><Year>2004</Year><IDText>Cancer risk and parental pesticide application in children of agricultural health study participants</IDText><DisplayText>(Flower et al., 2004)</DisplayText><record><dates><pub-dates><date>Apr</date></pub-dates><year>2004</year></dates><urls><related-urls><url><Go to ISI>;/000220770400054</url></related-urls></urls><titles><title>Cancer risk and parental pesticide application in children of agricultural health study participants</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><pages>631-

635</pages><number>5</number><contributors><authors><author>Flower, K.
B.</author><author>Hoppin, J. A.</author><author>Lynch, C. F.</author><author>Blair,
A.</author><author>Knott, C.</author><author>Shore, D. L.</author><author>Sandler, D.
P.</author></authors></contributors><added-date format="utc">1269462945</added-
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num><volume>112</volume></record></Cite></EndNote>].

One Canadian study (Pahwa et al. 2013) examined exposure to pesticides and soft tissue sarcoma in a case-control study and found no relation with use of glyphosate (OR 0.90 (95%CI 0.58-1.40)).

Brain Tumors (Glioma): Population-Based Case Control Studies: External to the AHS cohort study, HED identified population-based case control studies which evaluated brain cancer in relation to pesticides use. Glioma is the most common type of brain tumor. In a study of ever-use of pesticides, authors identified 251 glioma cases between 1988 and 1993 in Nebraska, and controls (n=498) identified from the same region. Matching for age and vital-status, study authors reported a non-significant elevated odds of glioma (OR 1.5 (95% CI (0.7, 3.1)) in relation to glyphosate use; however the results were significantly different between those who self-reported pesticide use (OR 0.4 (95% CI (0.1, 1.6)), and for those whom a proxy respondent was used (3.1 (95% CI (1.2, 8.2)), indicating recall bias was likely a characteristic of this study [ADDIN EN.CITE

<EndNote><Cite><Author>Lee</Author><Year>2005</Year><IDText>Agricultural pesticide use and risk of glioma in Nebraska, United States</IDText><DisplayText>(W. Lee et al., 2005)</DisplayText><record><dates><pub-dates><date>NOV 2005</date></pub-dates><year>2005</year></dates><keywords></keywords><isbn>1351-0711</isbn><work-type>Article</work-type><titles><title>Agricultural pesticide use and risk of glioma in Nebraska, United States</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><number>11</number><contributors><authors><author>Lee, WJ</author><author>Colt, JS</author><author>Heineman, EF</author><author>McComb, R</author><author>Weisenburger, DD</author><author>Lijinsky, W</author><author>Ward, MH</author></authors></contributors><language>English</language><added-date format="utc">1384789601</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Ward, MH (reprint author), NCI, Occupat & Environm Epidemiol Branch, Div Canc Epidemiol & Genet, 6120 Execut Blvd EPS 8104, Rockville, MD 20852 USANCI, Occupat & Environm Epidemiol Branch, Div Canc Epidemiol & Genet, Rockville, MD 20852 USAKorea Univ, Coll Med, Dept Prevent Med, Seoul 136701, South

KoreaUniv Nebraska, Med Ctr, Omaha, NE USA</auth-address><rec-number>5670</rec-number><last-updated-date format="utc">1384789601</last-updated-date><accession-num>WOS:000232932700008</accession-num><electronic-resource-num>10.1136/oem.2005.020230</electronic-resource-num><volume>62</volume></record></Cite></EndNote>]. Three other population-based case control studies of glioma risk were part of this literature review; authors investigated the question among men and also among women participating in the Upper Midwest Health Study ([ADDIN EN.CITE ADDIN EN.CITE.DATA]. Among glioma cases identified 1995-1997, authors found little evidence of a role of glyphosate in the etiology of this tumor. While herbicide use overall was non-statistically significantly linked to glioma in the study among men (OR 1.51 (95% CI (0.92, 2.48)), use of glyphosate was not linked to glioma among women (OR 0.7 (95% CI (0.4, 1.3). In the study by Carreon et al. (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to the study by Lee et al. (2005) noted above. Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (occupational use: OR 0.98 (95% CI 0.67, 1.43); home and garden use: OR 0.83 (95% CI 0.39, 1.73))[ADDIN EN.CITE <EndNote><Cite><Author>Yiin</Author><Year>2012</Year><IDText>The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma</IDText><DisplayText>(Yiin et al., 2012)</DisplayText><record><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/22691464</url></related-urls></urls><isbn>1476-069X</isbn><custom2>PMC3406961</custom2><titles><title>The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma</title><secondary-title>Environ Health</secondary-title></titles><pages>39</pages><contributors><authors><author>Yiin, J. H.</author><author>Ruder, A. M.</author><author>Stewart, P. A.</author><author>Waters, M. A.</author><author>Carreón, T.</author><author>Butler, M. A.</author><author>Calvert, G. M.</author><author>Davis-King, K. E.</author><author>Schulte, P. A.</author><author>Mandel, J. S.</author><author>Morton, R. F.</author><author>Reding, D. J.</author><author>Rosenman, K. D.</author><author>Brain Cancer Collaborative Study Group</author></authors></contributors><language>eng</language><added-date format="utc">1391104828</added-date><ref-type name="Journal Article">17</ref-type><dates><year>2012</year></dates><rec-number>5693</rec-number><last-updated-date format="utc">1391104828</last-updated-date><accession-num>22691464</accession-num><electronic-resource-num>10.1186/1476-069X-11-39</electronic-resource-

num><volume>11</volume></record></Cite></EndNote>]. Overall, this database presents little statistical evidence that there is a role for glyphosate in glioma risk in the Midwestern U.S.

Adenocarcinoma: Population-Based Case Control Study: In another population based case control study in the Midwest (NE), authors evaluated pesticide use and adenocarcinoma. Researchers did not observe an association between glyphosate exposure and either stomach cancer (OR (95% CI) 0.8 (0.4, 1.5)) or esophageal cancer (OR (95% CI) 0.7 (0.3, 1.4)) [ADDIN EN.CITE <EndNote><Cite><Author>Lee</Author><Year>2004</Year><IDText>Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus</IDText><DisplayText>(W. Lee et al., 2004)</DisplayText><record><dates><pub-dates><date>SEP 2004</date></pub-dates><year>2004</year></dates><keywords></keywords><isbn>1351-0711</isbn><work-type>Article</work-type><titles><title>Agricultural pesticide use and adenocarcinomas of the stomach and oesophagus</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>743-749</pages><number>9</number><contributors><authors><author>Lee, WJ</author><author>Lijinsky, W</author><author>Heineman, EF</author><author>Markin, RS</author><author>Weisenburger, DD</author><author>Ward, MH</author></authors></contributors><language>English</language><added-date format="utc">1384789530</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Ward, MH (reprint author), NCI, Occupat & Environm Epidemiol Branch, Div Canc Epidemiol & Genet, 6120 Execut Blvd, EPS 8104, Rockville, MD 20852 USANCI, Occupat & Environm Epidemiol Branch, Div Canc Epidemiol & Genet, Bethesda, MD 20892 USAUniv Nebraska, Med Ctr, Omaha, NE USA</auth-address><rec-number>5669</rec-number><last-updated-date format="utc">1384789530</last-updated-date><accession-num>WOS:000223398500004</accession-num><electronic-resource-num>10.1136/oem.2003.011858</electronic-resource-num><volume>61</volume></record></Cite></EndNote>]. Exposure assessment was based upon self-report pesticide use, with follow-up telephone interview to verify reported information. Cancer cases were identified through the state cancer registry, and confirmed by pathologist. While non-differential misclassification of either pesticide use could have occurred and attenuated or obscured results, it is unlikely there is a strong positive association with glyphosate and adenocarcinoma based the evidence presented in this study.

Non-Solid Tumor Sites (Lymphohematopoietic cancers)

There are several epidemiology studies of the possible link between pesticide use and lymphohematopoietic cancers; the study of NHL is particularly well represented in this small epidemiology database. All studies are case-control in design; there are no prospective cohort

evaluations of this potential association. The presence of case control study design across this database limits development of firm causal inference.

Leukemia: In a population-based case control study in Iowa and Minnesota, authors investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR (95% CI) 0.9 (0.5, 1.6)) [ADDIN EN.CITE <EndNote><Cite><Author>Brown</Author><Year>1990</Year><IDText>Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota</IDText><DisplayText>(Brown et al., 1990)</DisplayText><record><dates><pub-dates><date>Oct 15</date></pub-dates><year>1990</year></dates><keywords></keywords><isbn>0008-5472 (Print)0008-5472</isbn><titles><title>Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota</title><secondary-title>Cancer Res</secondary-title><alt-title>Cancer research</alt-title></titles><pages>6585-91</pages><number>20</number><contributors><authors><author>Brown, L. M.</author><author>Blair, A.</author><author>Gibson, R.</author><author>Everett, G. D.</author><author>Cantor, K. P.</author><author>Schuman, L. M.</author><author>Burmeister, L. F.</author><author>Van Lier, S. F.</author><author>Dick, F.</author></authors></contributors><edition>1990/10/15</edition><language>eng</language><added-date format="utc">1375291581</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, Maryland 20892.</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>5549</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>2208120</accession-num><volume>50</volume></record></Cite></EndNote>]. The study population was identified from cancers reported to state registry or authorities in 1981-1984, and pesticide exposure assessment was performed through in-person interview which authors state likely reduced exposure misclassification (incorrect exposure information). The large sample size (578 cases and 1245 controls), exposure assessment methods, and confounding variable control are strengths of the study; however the lack of clear exposure-response information and the potential for recall bias are also present. In another population based case control study, cases were identified in 1987-1992 through the Swedish cancer registry. Authors reported a non statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR (95% CI) 3.1 (0.8, 12.0), controlling for age, gender, and residential location [ADDIN EN.CITE <EndNote><Cite><Author>Nordstrom</Author><Year>1998</Year><IDText>Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study</IDText><DisplayText>(Nordstrom, Hardell, Magnuson, Hagberg, & Rask-Andersen, 1998)</DisplayText><record><dates><pub-dates><date>JUN 1998</date></pub-dates><year>1998</year></dates><keywords></keywords><isbn>0007-

0920</isbn><work-type>Article</work-type><titles><title>Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study</title><secondary-title>British Journal of Cancer</secondary-title></titles><pages>2048-2052</pages><number>11</number><contributors><authors><author>Nordstrom, M</author><author>Hardell, L</author><author>Magnuson, A</author><author>Hagberg, H</author><author>Rask-Andersen, A</author></authors></contributors><language>English</language><added-date format="utc">1384789682</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Nordstrom, M (reprint author), Orebro Med Ctr Hosp, Dept Oncol, S-70185 Orebro, SwedenOrebro Med Ctr Hosp, Dept Oncol, S-70185 Orebro, SwedenLinkoping Univ Hosp, Dept Occupat & Environm Med, S-58185 Linkoping, SwedenUniv Uppsala Hosp, Dept Oncol, S-75185 Uppsala, SwedenUniv Uppsala Hosp, Dept Occupat & Environm Med, S-75185 Uppsala, Sweden</auth-address><rec-number>5671</rec-number><last-updated-date format="utc">1384789682</last-updated-date><accession-num>WOS:000080207600054</accession-num><electronic-resource-num>10.1038/bjc.1998.341</electronic-resource-num><volume>77</volume></record></Cite></EndNote>]. However, these results are based on only 4 and 5 glyphosate exposed cases and controls, respectively, and should be interpreted with caution, as noted by the authors. At this time, the limited available literature concerning glyphosate use and leukemia cannot support a conclusion that glyphosate plays a role in leukemia.

Multiple Myeloma (MM): Using the same study population as noted above in reference to leukemia risk and pesticide use, Brown et al. (1993) studied whether pesticide use is also related to MM. Among men in Iowa (173 cases, 605 controls), authors observed a statistically non-significant elevated association with glyphosate use (OR (95% CI) 1.7 (0.80, 3.6))[ADDIN EN.CITE <EndNote><Cite><Author>Brown</Author><Year>1993</Year><IDText>Pesticide exposures and multiple myeloma in Iowa men.</IDText><DisplayText>(Brown, Burmeister, Everett, & Blair, 1993)</DisplayText><record><dates><pub-dates><date>Mar</date></pub-dates><year>1993</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/8481493</url></related-urls></urls><isbn>0957-5243</isbn><titles><title>Pesticide exposures and multiple myeloma in Iowa men.</title><secondary-title>Cancer Causes Control</secondary-title></titles><pages>153-6</pages><number>2</number><contributors><authors><author>Brown, L. M.</author><author>Burmeister, L. F.</author><author>Everett, G. D.</author><author>Blair, A.</author></authors></contributors><language>eng</language><added-date format="utc">1303932152</added-date><ref-type name="Journal Article">17</ref-

type><auth-address>Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, MD.</auth-address><rec-number>996</rec-number><last-updated-date format="utc">1303932152</last-updated-date><accession-num>8481493</accession-num><volume>4</volume></record></Cite></EndNote>]. However, authors caution that while the study may lend support for the role of pesticides in general, the study limitations preclude use of evidence in support of any one compound. In the AHS cohort analysis by de Roos et al. (2005), researchers also reported a non-statistically significantly elevated risk of multiple myeloma among glyphosate users (OR 2.6 (95% CI (0.70, 9.4)), but this results was based upon only 32 MM cases (20 of whom reported exposure to glyphosate), and authors did not observe evidence of an exposure-response trend by duration or intensity of pesticide use [ADDIN EN.CITE <EndNote><Cite><Author>De Roos</Author><Year>2005</Year><IDText>Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study</IDText><DisplayText>(De Roos et al., 2005)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2005</year></dates><keywords></keywords><isbn>0091-6765 (Print)0091-6765</isbn><custom2>Pmc1253709</custom2><titles><title>Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study</title><secondary-title>Environ Health Perspect</secondary-title><alt-title>Environmental health perspectives</alt-title></titles><pages>49-54</pages><number>1</number><contributors><authors><author>De Roos, A. J.</author><author>Blair, A.</author><author>Rusiecki, J. A.</author><author>Hoppin, J. A.</author><author>Svec, M.</author><author>Dosemeci, M.</author><author>Sandler, D. P.</author><author>Alavanja, M. C.</author></authors></contributors><edition>2005/01/01</edition><language>eng</language><added-date format="utc">1384293793</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Program in Epidemiology, Fred Hutchinson Cancer Research Center and the Department of Epidemiology, University of Washington, Seattle, Washington 98109, USA. deroos@u.washington.edu</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>5644</rec-number><last-updated-date format="utc">1384349385</last-updated-date><accession-num>15626647</accession-num><volume>113</volume></record></Cite></EndNote>]. Authors suggest there are too few cases of glyphosate exposed MM in the study to make a firm conclusion. In a population-based case control study in Canada, researchers reported non-statistically significantly elevated odds of MM in relation to glyphosate use (OR (95% CI) 1.22 (0.77, 1.93), based upon 32 and 133 glyphosate exposed MM case and controls, respectively [ADDIN EN.CITE <EndNote><Cite><Author>Pahwa</Author><Year>2012</Year><IDText>Multiple myeloma and exposure to pesticides: a Canadian case-control study</IDText><DisplayText>(Pahwa et al., 2012)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-

dates><year>2012</year></dates><keywords></keywords><isbn>1059-924x</isbn><titles><title>Multiple myeloma and exposure to pesticides: a Canadian case-control study</title><secondary-title>J Agromedicine</secondary-title><alt-title>Journal of agromedicine</alt-title></titles><pages>40-50</pages><number>1</number><contributors><authors><author>Pahwa, P.</author><author>Karunanayake, C. P.</author><author>Dosman, J. A.</author><author>Spinelli, J. J.</author><author>McDuffie, H. H.</author><author>McLaughlin, J. R.</author></authors></contributors><edition>2011/12/24</edition><language>eng</language><added-date format="utc">1374006867</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Canadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada. pup165@mail.usask.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>5519</rec-number><last-updated-date format="utc">1374006867</last-updated-date><accession-num>22191502</accession-num><electronic-resource-num>10.1080/1059924x.2012.632339</electronic-resource-num><volume>17</volume></record></Cite></EndNote>]. Using the same Canadian study population, Kachuri et al. (2013) further explored MM in relation to days per year used glyphosate and found that light users (≤ 2 days per year) had no association (OR 0.72 (95%CI 0.39-1.32)) where as heavy users (> 2 days per year) had a non-significant increased odds (OR 2.04 (95%CI (0.98-4.23))) Note, just as in the previous study, number of exposed cases and controls exposed to glyphosate were very low. Within the AHS study population, molecular epidemiology researchers studied the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS); MGUS is considered a pre-clinical marker of MM progression. Authors did not observe a link with glyphosate use in the AHS cohort (OR 0.50 (95% CI (0.20, 1.0)) [ADDIN EN.CITE <EndNote><Cite><Author>Landgren</Author><Year>2009</Year><IDText>Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study</IDText><DisplayText>(Landgren et al., 2009)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>;//000267147400021</url></related-urls></urls><titles><title>Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study</title><secondary-title>Blood</secondary-title></titles><pages>6386-6391</pages><number>25</number><contributors><authors><author>Landgren, O.</author><author>Kyle, R. A.</author><author>Hoppin, J. A.</author><author>Freeman, L. E. B.</author><author>Cerhan, J. R.</author><author>Katzmann, J. A.</author><author>Rajkumar, S. V.</author><author>Alavanja, M.

C.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>20</rec-number><last-updated-date format="utc">1384972707</last-updated-date><accession-num>ISI:000267147400021</accession-num><electronic-resource-num>10.1182/blood-2009-02-203471</electronic-resource-num><volume>113</volume></record></Cite></EndNote>]. At this time, the epidemiologic database regarding the possible link between pesticide use and MM is too small and inconsistent to determine whether glyphosate plays a role in this cancer.

Lymphoma: The National Cancer Institute (NCI) performed a series of population-based case control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred NHL cases and controls, identified cases through disease registries which in many cases were histopathologically confirmed. Investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time. Early investigations (IA and MN) did not observe a link with ever-use of glyphosate (OR (95% CI) 1.0 (0.5, 2.2)); however authors did not adjust for exposure to other pesticides in this study [ADDIN EN.CITE <EndNote><Cite><Author>Cantor</Author><Year>1992</Year><IDText>Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota</IDText><DisplayText>(Cantor et al., 1992)</DisplayText><record><dates><pub-dates><date>May 1</date></pub-dates><year>1992</year></dates><keywords></keywords><isbn>0008-5472 (Print)0008-5472</isbn><titles><title>Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota</title><secondary-title>Cancer Res</secondary-title><alt-title>Cancer research</alt-title></titles><pages>2447-55</pages><number>9</number><contributors><authors><author>Cantor, K. P.</author><author>Blair, A.</author><author>Everett, G.</author><author>Gibson, R.</author><author>Burmeister, L. F.</author><author>Brown, L. M.</author><author>Schuman, L.</author><author>Dick, F. R.</author></authors></contributors><edition>1992/05/01</edition><language>eng</language><added-date format="utc">1373466565</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, National Cancer Institute, Bethesda, Maryland 20892.</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>4699</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>1568215</accession-num><volume>52</volume></record></Cite></EndNote>]. Pooling data from several Midwestern states to increase study sample size (IA, MN, NE), and using additional pesticide use information to adjust the risk estimate (duration and frequency of use, telephone follow-up interview), Lee et al. (2004) observed a positive, non-significant association with glyphosate among those without asthma (OR (95% CI) 1.4 (0.98, 2.1)), adjusting for age, state and vital

status [ADDIN EN.CITE

<EndNote><Cite><Author>Lee</Author><Year>2004</Year><IDText>Non-Hodgkin's lymphoma among asthmatics exposed to pesticides</IDText><DisplayText>(W. J. Lee et al., 2004)</DisplayText><record><dates><pub-dates><date>Aug 20</date></pub-dates><year>2004</year></dates><keywords></keywords><isbn>0020-7136 (Print)0020-7136</isbn><titles><title>Non-Hodgkin's lymphoma among asthmatics exposed to pesticides</title><secondary-title>Int J Cancer</secondary-title><alt-title>International journal of cancer. Journal international du cancer</alt-title></titles><pages>298-302</pages><number>2</number><contributors><authors><author>Lee, W. J.</author><author>Cantor, K. P.</author><author>Berzofsky, J. A.</author><author>Zahm, S. H.</author><author>Blair, A.</author></authors></contributors><edition>2004/06/16</edition><language>eng</language><added-date format="utc">1374006867</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics National Cancer Institute, National Institutes of Health, Rockville, MD 20852, USA. Leewj@mail.nih.gov</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>5516</rec-number><last-updated-date format="utc">1374006867</last-updated-date><accession-num>15197786</accession-num><electronic-resource-num>10.1002/ijc.20273</electronic-resource-num><volume>111</volume></record></Cite></EndNote>]. In a pooled analysis (n=3,417) of these same three study states, and utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, authors observed a similarly elevated, but non-statistically significant result: OR (95% CI) 1.6 (0.90, 2.8) [ADDIN EN.CITE

<EndNote><Cite><Author>De Roos</Author><Year>2003</Year><IDText>Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men</IDText><DisplayText>(De Roos et al., 2003)</DisplayText><record><dates><pub-dates><date>Sep</date></pub-dates><year>2003</year></dates><urls><related-urls><url><Go to ISI>;//000184904000029</url></related-urls></urls><titles><title>Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><number>9</number><contributors><authors><author>De Roos, A. J.</author><author>Zahm, S. H.</author><author>Cantor, K. P.</author><author>Weisenburger, D. D.</author><author>Holmes, F. F.</author><author>Burmeister, L. F.</author><author>Blair, A.</author></authors></contributors><added-date format="utc">1269462945</added-date><ref-type name="Journal Article">17</ref-type><rec-number>145</rec-number><last-

updated-date format="utc">1269462945</last-updated-date><accession-num>ISI:000184904000029</accession-num><electronic-resource-num>e11</electronic-resource-num><volume>60</volume></record></Cite></EndNote>]. These three evaluations reflect the same study population, use different levels of information (duration and frequency of exposure) and different analytic techniques (hierarchical regression and stratified analysis (by atopy)). While studies with increasing levels of refinement to method report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

Hardell et al. (1999 and 2002) performed two analyses of the possible link between pesticide use and NHL using the Swedish cancer registry and a telephone based exposure questionnaire to determine pesticide use. The initial investigation of 404 NHL cases and 741 control subjects included only 4 and 5 glyphosate exposed cases and controls, respectively. The risk estimate was elevated, but precision was low (OR (95% CI) 2.3 (0.40, 13.0)) [ADDIN EN.CITE <EndNote><Cite><Author>Hardell</Author><Year>1999</Year><IDText>A case-control study of non-Hodgkin lymphoma and exposure to pesticides</IDText><DisplayText>(L Hardell & Eriksson, 1999)</DisplayText><record><dates><pub-dates><date>MAR 15 1999</date></pub-dates><year>1999</year></dates><keywords></keywords><isbn>0008-543X</isbn><work-type>Article</work-type><titles><title>A case-control study of non-Hodgkin lymphoma and exposure to pesticides</title><secondary-title>Cancer</secondary-title></titles><pages>1353-1360</pages><number>6</number><contributors><authors><author>Hardell, L</author><author>Eriksson, M</author></authors></contributors><language>English</language><added-date format="utc">1384789741</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Hardell, L (reprint author), Orebro Med Ctr, Dept Oncol, S-70185 Orebro, SwedenOrebro Med Ctr, Dept Oncol, S-70185 Orebro, SwedenUniv Lund Hosp, Dept Oncol, S-22185 Lund, Sweden</auth-address><rec-number>5672</rec-number><last-updated-date format="utc">1384789741</last-updated-date><accession-num>WOS:000079092900019</accession-num><electronic-resource-num>10.1002/(SICI)1097-0142(19990315)85:6<1353::AID-CNCR19>3.0.CO;2-1</electronic-resource-num><volume>85</volume></record></Cite></EndNote>]. In a pooled analysis reflecting the same study time period and prevalence of glyphosate use, Hardell et al. (2002) reported a non-statistically elevated odds of NHL among glyphosate users: OR (95% CI) 1.85 (0.55, 6.20)), however this estimate also lacks precision [ADDIN EN.CITE <EndNote><Cite><Author>Hardell</Author><Year>2002</Year><IDText>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies</IDText><DisplayText>(L. Hardell et al., 2002)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2002</year></dates><keywords></keywords><isbn>1042-8194

(Print)1026-8022</isbn><titles><title>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies</title><secondary-title>Leuk Lymphoma</secondary-title><alt-title>Leukemia & lymphoma</alt-title></titles><pages>1043-9</pages><number>5</number><contributors><authors><author>Hardell, L.</author><author>Eriksson, M.</author><author>Nordstrom, M.</author></authors></contributors><edition>2002/08/01</edition><language>eng</language><added-date format="utc">1384293793</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Department of Oncology, Orebro University Hospital, Sweden. lennart.hardell@orebroll.se</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>5652</rec-number><last-updated-date format="utc">1384349385</last-updated-date><accession-num>12148884</accession-num><volume>43</volume></record></Cite></EndNote>]. Authors stated glyphosate use was low in the time period of the study 1987-1990. Therefore, authors performed a new study in later time period (1999-2003) in which glyphosate use had increased. In this study, authors observed a similar risk estimate (OR (95% CI) 1.55 (0.77, 2.94)), among 910 NHL cases and 1016 non-NHL controls [ADDIN EN.CITE <EndNote><Cite><Author>Eriksson</Author><Year>2008</Year><IDText>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</IDText><DisplayText>(Eriksson et al., 2008)</DisplayText><record><dates><pub-dates><date>Oct</date></pub-dates><year>2008</year></dates><urls><related-urls><url><Go to ISI>;//000258892500023</url></related-urls></urls><titles><title>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</title><secondary-title>International Journal of Cancer</secondary-title></titles><pages>1657-1663</pages><number>7</number><contributors><authors><author>Eriksson, M.</author><author>Hardell, L.</author><author>Carlberg, M.</author><author>Akerman, M.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>32</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>ISI:000258892500023</accession-num><electronic-resource-num>10.1002/ijc.23589</electronic-resource-num><volume>123</volume></record></Cite></EndNote>]. Authors conclude that the follow-up study, with a greater number of glyphosate exposed participants lends support to the conclusion glyphosate may play a role in NHL.

Within the Cross- Canada study of pesticides and health, authors estimated the association between glyphosate and NHL as well. These investigations reflect cases identified 1991-1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of

cases, and implemented a two-tiered exposure questionnaire, and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the study results. Glyphosate was not among the primary findings of either study. The initial study within this population identified a non-statistically significant 20% increased risk of NHL (OR (95% CI) 1.20 (0.83, 1.74)) [ADDIN EN.CITE

<EndNote><Cite><Author>McDuffie</Author><Year>2001</Year><IDText>Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health</IDText><DisplayText>(McDuffie et al., 2001)</DisplayText><record><dates><pub-dates><date>Nov</date></pub-dates><year>2001</year></dates><keywords></keywords><isbn>1055-9965 (Print)1055-9965</isbn><titles><title>Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health</title><secondary-title>Cancer Epidemiol Biomarkers Prev</secondary-title><alt-title>Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology</alt-title></titles><pages>1155-63</pages><number>11</number><contributors><authors><author>McDuffie, H. H.</author><author>Pahwa, P.</author><author>McLaughlin, J. R.</author><author>Spinelli, J. J.</author><author>Fincham, S.</author><author>Dosman, J. A.</author><author>Robson, D.</author><author>Skinnider, L. F.</author><author>Choi, N. W.</author></authors></contributors><edition>2001/11/09</edition><language>eng</language><added-date format="utc">1373471384</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Centre for Agricultural Medicine, University of Saskatchewan, Saskatoon, Saskatchewan. mcduffie@sask.usask.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>5452</rec-number><last-updated-date format="utc">1373471384</last-updated-date><accession-num>11700263</accession-num><volume>10</volume></record></Cite></EndNote>], which attenuated in a follow-up study which controlled for exposure to other pesticides (OR (95% CI) 0.92 (0.54, 1.55)) [ADDIN EN.CITE

<EndNote><Cite><Author>Hohenadel</Author><Year>2011</Year><IDText>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</IDText><DisplayText>(Hohenadel et al., 2011)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2011</year></dates><keywords></keywords><isbn>1660-4601</isbn><custom2>Pmc3138027</custom2><titles><title>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</title><secondary-title>Int J Environ Res Public Health</secondary-title><alt-title>International journal of environmental research and public health</alt-title></titles><pages>2320-30</pages><number>6</number><contributors><authors><author>Hohenadel,

K. /author><author>Harris, S. A. /author><author>McLaughlin, J. R. /author><author>Spinelli, J. J. /author><author>Pahwa, P. /author><author>Dosman, J. A. /author><author>Demers, P. A. /author><author>Blair, A. /author></authors></contributors><edition>2011/07/22</edition><language>eng</language><added-date format="utc">1373466563</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Occupational Cancer Research Centre, 505 University Avenue, 14th floor, Toronto, Ontario M5G 1X3, Canada. karin.hohenadel@cancercare.on.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>4600</rec-number><last-updated-date format="utc">1373467057</last-updated-date><accession-num>21776232</accession-num><electronic-resource-num>10.3390/ijerph8062320</electronic-resource-num><volume>8</volume></record></Cite></EndNote>]. Within this series of studies, authors also evaluated Hodgkin lymphoma (HL), and similarly observed little statistical evidence of an association, using similar study design and methods (OR (95% CI) 0.99 (0.62, 1.18)) [ADDIN EN.CITE <EndNote><Cite><Author>Karunanayake</Author><Year>2012</Year><IDText>Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study</IDText><DisplayText>(Karunanayake et al., 2012)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2012</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/22191501</url></related-urls></urls><isbn>1545-0813</isbn><titles><title>Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study</title><secondary-title>J Agromedicine</secondary-title></titles><pages>30-9</pages><number>1</number></contributors><authors><author>Karunanayake, C. P. /author><author>Spinelli, J. J. /author><author>McLaughlin, J. R. /author><author>Dosman, J. A. /author><author>Pahwa, P. /author><author>McDuffie, H. H. /author></authors></contributors><language>eng</language><added-date format="utc">1391104896</added-date><ref-type name="Journal Article">17</ref-type><rec-number>5694</rec-number><last-updated-date format="utc">1391104896</last-updated-date><accession-num>22191501</accession-num><electronic-resource-num>10.1080/1059924X.2012.632726</electronic-resource-num><volume>17</volume></record></Cite></EndNote>]. In a separate study using a hospital-based case control study design (France (2000-04)), authors identified 491 NHL cases and 456 non-cases, and performed telephone-based questionnaire to assess pesticide and other confounding variables. Investigators did not observe an association between NHL and glyphosate use (OR (95% CI) 1.0 (0.50, 2.2)) [ADDIN EN.CITE <EndNote><Cite><Author>Orsi</Author><Year>2009</Year><IDText>Occupational exposure to

pesticides and lymphoid neoplasms among men: results of a French case-control study</IDText><DisplayText>(Orsi et al., 2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>;//000265274700003</url></related-urls></urls><titles><title>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>291-298</pages><number>5</number><contributors><authors><author>Orsi, L.</author><author>Delabre, L.</author><author>Monnereau, A.</author><author>Delval, P.</author><author>Berthou, C.</author><author>Fenau, P.</author><author>Marit, G.</author><author>Soubeyran, P.</author><author>Huguet, F.</author><author>Milpied, N.</author><author>Leporrier, M.</author><author>Hemon, D.</author><author>Troussard, X.</author><author>Clavel, J.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>22</rec-number><last-updated-date format="utc">1384972839</last-updated-date><accession-num>ISI:000265274700003</accession-num><electronic-resource-num>10.1136/oem.2008.040972</electronic-resource-num><volume>66</volume></record></Cite></EndNote>].

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and lymphoma, B-cell lymphoma and subtypes (Cocco et al. 2013). Although the study recruited 2348 cases and 2462 controls, very small number of cases (n=4) and controls (n=2) were exposed to glyphosate. A non-significant increase in odds was observed for B-cell lymphoma, but the estimate is unstable due to small number of exposed cases and controls (OR 3.1(95%CI 0.6-17.1).

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL utilizing six of the above mentioned studies (McDuffie et al. 2001; Hardell et al. 2002; DeRoos et al. 2003 and 2005; Eriksson et al. 2008; and Orsi et al. 2009) yielding a meta risk ratio of 1.5 (95%CI 1.1-2.0). This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences. However, the IARC Working Group noted that two of the studies' fully adjusted risk estimates were not used in this analysis and conducted a reexamination of the results by estimating the meta risk ratio to be 1.3 (95%CI 1.03-1.65) (IARC 2015).

Based on the literature in the database, there is limited evidence of an association between glyphosate and NHL. Most of the studies were under powered to detect significant associations. However, several studies have reported elevated associations, although imprecise and not

significant. The meta-analysis by Schinasi and Leon brings together those studies to strengthen the analyses and finds slightly elevated risks.

Glyphosate Cancer Summary

Most studies were hypothesis-generating in nature, small sample sizes with limited power to detect associations, and study authors evaluated use of glyphosate in addition to several other pesticides. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis limit epidemiologic inference. For most cancers examined in this database, glyphosate was not associated with adverse outcome. However, across the several population-based case-control studies on NHL and pesticide use, some investigators observed non-statistically significantly increased risk in relation to glyphosate use, while others reported no observation of a statistical association with glyphosate use. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could explain these inconsistencies in the data. A meta-analysis incorporated six of those NHL studies and found a slightly elevated statistically significant meta risk-ratio. Therefore, based on this current human epidemiologic literature database, there is limited evidence in the role of glyphosate and cancer, primarily with NHL.

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Message

From: Kathryn Guyton [GuytonK@iarc.fr]
Sent: 7/9/2014 3:37:28 PM
To: Rowland, Jess [Rowland.Jess@epa.gov]
Subject: Re: Pesticide carcinogenicity

Importance: High

Bonjour Jess!

Apologies for the delay in getting back to you on this, I've been out of the office. I hope you are doing well and enjoying the summer thus far!

I wanted to thank you again for providing all of this detailed information on chlorpyrifos. It's really helpful to have the data to examine.

We are interested in the carcinogenicity and mutagenicity data for several other pesticides, specifically diazinon, glyphosate, malathion, acephate, tetrachlorvinos and parathion. Would it be possible to ask EPA to post any relevant documents (including DERs, Cancer Assessment Review Committee memos, and REDs for carcinogenicity, mutagenicity and any relevant toxicity studies) on the EPA public website e.g., <http://www.epa.gov/oppsrrd1/reregistration/status.htm>? Would I need to request this via FOIA or is there another mechanism?

Many thanks for your assistance,
Best regards,
Kate
Kate Z. Guyton PhD DABT

Monographs Section

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Guytonk@iarc.fr

From: <Rowland>, Jess <Rowland.Jess@epa.gov>
Date: Thursday 19 June 2014 21:01
To: Kate Guyton <guytonk@iarc.fr>
Subject: RE: Pesticide carcinogenicity

Hi Kate

All the animals (males and females) were examined.

At the initiation of the study, there were 59 males and 59 females/dose group.

In the Table 18, the data are presented in three time periods [one year (week 52); 1.5 year (week 78) and at sacrifice (week 82) as follows:

Males (No. Examined)					
Study Weeks	Group 1	Group 2	Group 3	Group 3	Page Number
1 – 52	14	12	8	4	263
53-78	14	21	14	6	265
79-82	31	26	37	49	268
Total Examined	59	59	59	59	
Females (No. Examined)					
1-52	4	1	3	4	264
53-78	7	5	9	9	266
79-82	48	53	47	46	270
Total Examined	59	59	59	59	

Hope this helps

Regards

JR

Jess Rowland,
Deputy Director
Health Effects Division

Ex. 6 Personal Privacy (PP)

From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Thursday, June 19, 2014 12:30 PM

To: Rowland, Jess

Subject: Re: Pesticide carcinogenicity

Importance: High

Bonjour Jess!

Thank you so much for the information. Am I correct in the interpretation that not all of the male animals were examined? If so, is the full incidence data obtainable?

Thanks again,

Best,

Kate

Kate Z. Guyton PhD DABT

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Guytonk@iarc.fr

From: <Rowland>, Jess <Rowland.Jess@epa.gov>

Date: Thursday 19 June 2014 17:43

To: Kate Guyton <guytonk@iarc.fr>

Subject: RE: Pesticide carcinogenicity

Hi Kate

Hope all is well.

As per my previous note, I got the study report and am attaching the Table 18 which has the summary data of the tumors observed in the mouse carcinogenicity study.

Sorry about the poor quality of the report....it is 26 years old !!!

I am also attaching the Data Evaluation Recored of the carcinogenicity study in mice which has the summary data of the non-neoplastic lesions.

Let me know if u need additional info.

Regards

JR

Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Tuesday, June 03, 2014 3:00 AM

To: Rowland, Jess

Subject: Re: Pesticide carcinogenicity

Good morning Jess,

This is extremely helpful-- much appreciated! Will look forward to the update.

Best regards,
Kate

Envoyé de mon iPhone

On 02 Jun 2014, at 20:46, "Rowland, Jess" <Rowland.Jess@epa.gov> wrote:

Hi Kate

I reviewed the DER of the mouse study and it does not include the tumor table.
I have ordered the original study report to get the data
And will send them to you as soon as I get it

Regards

JR

Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Thursday, May 29, 2014 8:46 AM

To: Eiden, Catherine

Cc: Rowland, Jess

Subject: Re: Pesticide carcinogenicity

Thanks so much, Catherine! We may have some questions on current use of OPs and will forward a list of particular agents of interest in the next week or so.

Jess- would appreciate if you could provide any insight on the chlorpyrifos bioassay data (see below).

Many thanks and best wishes from Lyon,
Kate

Envoyé de mon iPhone

On 28 May 2014, at 19:31, "Eiden, Catherine" <Eiden.Catherine@epa.gov> wrote:

Hi Kathryn,

Jess Rowland @ EPA's Office of Pesticide Programs is your Point of Contact (POC) for toxicity (cancer) information on the pesticides.

Is there anything else we can help with @ this point on the exposure side of things?

Catherine Eiden
Senior Advisor, ESA & MBTA
Pesticide Re-evaluation Division
Office of Pesticide Programs
USEPA

Ex. 6 Personal Privacy (PP)

From: Kathryn Guyton [mailto:GuytonK@iarc.fr]
Sent: Thursday, May 22, 2014 12:32 PM
To: Eiden, Catherine
Subject: Re: Pesticide carcinogenicity

Hi Catherine,

In looking further at the OP class, I find the following summary of the chlorpyrifos carcinogenicity data: "Even though neoplastic lesions were observed in both sexes of mice, the study showed that chlorpyrifos does not have an oncogenic potential". See below.

However, the report available here: <http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/059101/059101-352.pdf> does not list the incidence of these tumours, which is somewhat curious, given that the incidence and statistical analyses of non-neoplastic lesions are provided?

Is it possible to obtain the tumor incidence information, from the mouse as well as the rat studies? There is a study referenced below, and I am not sure if it is the same pdf with the limited information, or if indeed one exists that would provide the tumor incidence data.

Many thanks,
Kate
Kate Z. Guyton PhD DABT
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International Agency for Research on Cancer
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France
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Guytonk@iarc.fr

870.4200b Carcinogenicity (Feeding) – Mouse

This study evaluated the oncogenic potential of test compound, at dietary concentrations of 0, 5.0, 50 or 250 ppm chlorpyrifos (equivalent to approximately: 0, 0.89, 8.84, or 45.2 mg/kg/d (M); and 0, 0.938, 9.79, or 48.1 mg/kg/d (F), respectively) when administered to CD-1 mice for 78 weeks (MRID 42534201).

Systemic toxicity was observed in high-dose animals and included decreased body weight and feed consumption in males, lower mean water consumption in

females, increased incidence of gross clinical findings (ocular opacity, hair loss on head and around eyes) and non-neoplastic lesions (keratitis, hepatocytic fatty vacuolation) in high dose males & females. Neoplastic lesions were observed in both sexes, but were not considered to be treatment-related. Plasma cholinesterase activities were significantly reduced at all treatment levels; brain activities were significantly decreased only in the high-dose animals.

From: <Eiden>, Catherine <Eiden.Catherine@epa.gov>

Date: Tuesday 20 May 2014 23:34

To: Kate Guyton <guytonk@iarc.fr>

Subject: RE: Pesticide carcinogenicity

Bonjour Kathryn! I think the selection of pesticides is interesting. I would have

Ex. 5 Deliberative Process (DP)

email to our senior toxicologists who work on cancer and get their take. I am sorry it took me a few days to get to your message; I was out of the office last week.

Catherine Eiden
Senior Advisor, ESA & MBTA
Pesticide Re-evaluation Division
Office of Pesticide Programs

USEPA

Ex. 6 Personal Privacy (PP)

From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Wednesday, May 14, 2014 4:43 AM

To: Eiden, Catherine

Subject: Re: Pesticide carcinogenicity

Bonjour Catherine!

I hope all is well in Washington. We recently hosted our Advisory Group meeting here in Lyon and they accorded high priority to several pesticides/classes for IARC evaluation. Attached is a summary report.

For the upcoming volume 112 meeting in March 2015, we are considering the organophosphates as a good start for the pesticides, given the numerous priorities identified in this class.

Ex. 5 Deliberative Process (DP)

I'd be interested in your thoughts on particular agents to include, as well as any suggestions you may have for experts to include on the Working Group.

Best wishes from Lyon,

Kate

Kate Z. Guyton PhD DABT

Monographs Section

International Agency for Research on Cancer
150, cours Albert Thomas
69372 Lyon Cedex 08

France

Tel: [+33] (0)4 72 73 86 54

Guytonk@iarc.fr

From: Eiden, Catherine [<mailto:Eiden.Catherine@epa.gov>]

Sent: 21 March 2014 20:52

To: Kathryn Guyton

Subject: RE: Pesticide carcinogenicity

Bonjour! I see you are getting into the swing of things!

Yes, let's wait until you have a clearer idea of the meeting topic. On the toxicity side of things - the Office of Pesticides has a lot of data and reviews of data that we use in making safety findings before licensing pesticide products. Much of this is internal and not on a public website. We also have access to epidemiological study data from National Institutes of Health that may be of interest as it is specific to pesticides and cancers. That information would be publically available as well. On the exposure side of

things we have experience determining what the main sources of exposure to a pesticide are and how much exposure is likely. Information on production volume is probably going to be considered Confidential Business information (CBI) and is not publically shared, but protected under FIFRA (pesticide statute). But we should have information on usage from some publically available data bases and have staff here that could help with that.

I look forward to speaking to you again. Keep me posted on your progress, and enjoy France in the springtime!

Cheers!

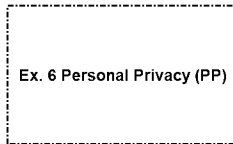
Catherine Eiden

Senior Advisor, ESA & MBTA

Pesticide Re-evaluation Division

Office of Pesticide Programs

USEPA



From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Friday, March 21, 2014 12:02 PM

To: Eiden, Catherine

Subject: RE: Pesticide carcinogenicity

Bonjour Catherine!

Thanks so much for the information. We have posted the general IARC meeting notification, see volume 112 at <http://monographs.iarc.fr/ENG/Meetings/index.php>. However, we are in the process of

further narrowing the meeting topic. In the next month or two, I expect to be able provide greater specificity with regard to the pesticides or groups to be evaluated. Would it be helpful to await that before investigating potential meeting participants further?

The link below is very helpful! In addition, information on production volume that may inform total usage/exposure would be helpful (again, perhaps especially once we refine the list of agents).

I hope you will consider participating on the working group for the volume 112 meeting, which will be 3-10 March in Lyon, France. You can access this link for more information on what is required for self nomination:

<http://monographs.iarc.fr/ENG/Meetings/vol112-callexperts.php>. Happy to discuss this further if it may be of interest and possible for you to participate.

Thank you again!

Best regards,

Kate

Kate Z. Guyton PhD DABT

Monographs Section

International Agency for Research on Cancer

150, cours Albert Thomas

69372 Lyon Cedex 08

France

Tel: [+33] (0)4 72 73 86 54

Guytonk@iarc.fr

From: Eiden, Catherine [mailto:Eiden.Catherine@epa.gov]

Sent: 21 March 2014 14:46

To: Kathryn Guyton

Subject: RE: Pesticide carcinogenicity

Hi Kathryn,

Could you send me the names of the pesticides that have been identified by IARC for evaluation? That would help me narrow my search with respect to available information on mechanistic studies. I have contacts here in the US for toxicology experts (Edward Scollon (eco and human health perspective) and Anna Lowit (human health perspective) and exposure experts (myself and David Miller) and the UK and EFSA regarding pesticides in general, but specific chemical names would be helpful if you have them.

I will contact my UK colleagues and ask them for ideas on databases and names of potential working group members.

Below is a link to databases in the EU on pesticides. You may have this already. Is this the kind of information you are looking for in terms of databases, or something different.

http://www.eppo.int/PPPRODUCTS/information/information_ppp.htm

I would be happy to serve on a working group, but would specifics to clear it with my managers.

Thank you!

Catherine Eiden

Senior Advisor, ESA & MBTA

Pesticide Re-evaluation Division

Office of Pesticide Programs

USEPA



From: Kathryn Guyton [<mailto:GuytonK@iarc.fr>]

Sent: Tuesday, March 11, 2014 12:53 PM

To: Eiden, Catherine

Subject: Pesticide carcinogenicity

Hello Catherine!

I received your contact information from Matt Lorber, a mutual colleague at EPA. By way of introduction, I recently separated from EPA to join the IARC monograph programs in Lyon, France (<http://monographs.iarc.fr/>). Matt tells me you have had considerable international experience and might be able to help identify expert(s) in pesticide exposure, carcinogenicity and/or mechanisms both in the US and abroad.

IARC has received a number of nominations to evaluate the carcinogenicity of pesticides. Some have been classified previously for carcinogenicity by IARC (<http://monographs.iarc.fr/ENG/Classification/index.php>). Others have been evaluated in the US by EPA (http://npic.orst.edu/chemicals_evaluated.pdf) and NTP (<http://ntp.niehs.nih.gov/?objectid=03C9F0A4-B1C2-31DE-ABA8508AE9949C57>), whereas many have not yet been classified for carcinogenicity by any authoritative body.

I'm interested in gathering information on which compounds or classes may have considerable exposure from the global perspective. In addition, it would be useful to learn which may have appropriate database of animal bioassay and/or supporting mechanistic studies to support an IARC evaluation, recognizing that the individual animal data for the bioassays is often proprietary and not available to the public (but

could potentially be sought under a FOIA request). In these contexts, any individuals, including yourself, who might be willing to share their perspectives and/or have the potential to serve on an upcoming IARC monographs working group-- would be valuable to identify.

If I can clarify, do let me know.

Thank you!

Kate

Kate Z. Guyton PhD DABT

Monographs Section

International Agency for Research on Cancer
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France
Tel: [+33] (0)4 72 73 86 54

Guytonk@iarc.fr

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Message

From: Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]
Sent: 4/6/2015 1:28:16 PM
To: May, Brenda [May.Brenda@epa.gov]; Rowland, Jess [Rowland.Jess@epa.gov]
Subject: Glyphosate

Hi Brenda and Jess,

Good Morning!

Just wanted to get your thoughts on the Glyphosate assessment. Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP) When will OPP assess glyphosate as part of registration review? Do you foresee an impact in the OPP evaluation?

Please let me know.

Thanks.

Santhini

Message

From: Housenger, Jack [Housenger.Jack@epa.gov]
Sent: 3/21/2015 2:41:56 AM
To: Rowland, Jess [Rowland.Jess@epa.gov]
Subject: Re: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)

Thanks

Sent from my iPhone

On Mar 20, 2015, at 8:12 PM, Rowland, Jess <Rowland.Jess@epa.gov> wrote:

Hi Jack
Fyi.....

Sent from my Windows Phone

From: [Miller, David](#)
Sent: 3/20/2015 2:53 PM
To: [OPP HED](#)
Subject: FW: Lancet Oncology IARC summary
(malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)

FYI – for those with an interest, the attached is the recently released IARC summary report on findings for malathion/diazinon/ glyphosate/ tetrachlorpvinphos/parathion.

The WHO/IARC graphic below shows how the 2A (malathion, diazinon, and glyphosate) and 2B (tetrachlorvinphos and parathion) group classifications were derived based on the animal and human epi results reviewed by the IARC Panel.

<image003.png>
David

-----Original Message-----

From: Miller, David
Sent: Friday, March 20, 2015 1:57 PM
To: Christensen, Carol; Britton, Wade; Rowland, Jess
Cc: Vogel, Dana
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Thanks, Carol.

I've attached the downloaded PDF of the article to make it simpler for folks.

David.

-----Original Message-----

From: Christensen, Carol
Sent: Friday, March 20, 2015 1:24 PM
To: Britton, Wade; Miller, David; Rowland, Jess

Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI: [http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(15\)70134-8.pdf](http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf)

From: Christensen, Carol

Sent: Friday, March 20, 2015 11:53 AM

To: Britton, Wade; Miller, David; Rowland, Jess

Subject: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Hi All

I just learned that the summary of the IARC-pesticide meeting is expected to be available on line around 1 pm today. FYI.

I think this is the link: <http://www.thelancet.com/journals/lanonc/issue/current>.

Carol

<Lancet Onco. Carcinogenicity of tetrachlorvinphos, parathion, malathion....pdf>

Message

From: Lobdell, Danelle [Lobdell.Danelle@epa.gov]
Sent: 8/20/2015 2:59:56 PM
To: Rowland, Jess [Rowland.Jess@epa.gov]
Subject: RE: Glyphosate CARC document
Attachments: GLYPHOSATE_Summ Table_52.xlsx; Glyphosate_TierII_2_5_14 (Autosaved).docx

Here is the Tier II write up and the epi table

Danelle

Danelle T. Lobdell, Ph.D., M.S.
Epidemiologist
National Health and Environmental Effects Research Laboratory
Environmental Public Health Division
Mail:
USEPA
MD 58A
Research Triangle Park, NC 27711
Package Delivery:
USEPA Human Studies Facility
104 Mason Farm Rd, Room 52
Chapel Hill, NC 27514-4512
Phone: 919-843-4434 **Fax:** 919-966-7584

From: Rowland, Jess
Sent: Thursday, August 20, 2015 9:42 AM
To: Lobdell, Danelle
Subject: Glyphosate CARC document
Importance: High

Hi Danelle

Here is the outline for the Epi section of the CARC document.
I have put in some text to lead into your assessment.
I am free from 10:30 to 11:00 am. Is this a suitable time for us to discuss...

Thanks

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

Message

From: Smith, Charles [Smith.Charles@epa.gov]
Sent: 2/4/2015 11:51:54 AM
To: Knorr, Michele [knorr.michele@epa.gov]; Goerke, Ariadne [Goerke.Ariadne@epa.gov]; Wakefield, Benjamin J. [wakefield.benjamin@epa.gov]
CC: Rowland, Jess [Rowland.Jess@epa.gov]
Subject: FW: HED RAs
Attachments: D267588.MEM.pdf; 417300.001.pdf

Our support staff were able to find two corn RA documents. You can even see a huge difference between the first one which was 1997 and the second one which is form 2000. It is hard to tell as there is no mention of the terms "genetically modified" but I believe the 417300 doc is the original (First Gen RoundUp Ready) corn document while 267588 is a revised corn document (Second Gen RoundUp Ready). The revised document talks specifically about how this is the Second Gen in the residue chemistry section.

Charles "Billy" Smith
Branch Chief RAB1
Health Effects Division
Office of Pesticide Programs
703-305-0291

From: Rowland, Jess
Sent: Tuesday, February 03, 2015 9:29 PM
To: Smith, Charles; May, Brenda
Subject: FW: HED RAs

Billy
Here you go....send it to Michele.
Bren
Thanks so much ☺. Can you please find my sanity!!!

Sent from my Windows Phone

From: May, Brenda
Sent: 2/3/2015 4:10 PM
To: Rowland, Jess
Subject: RE: HED RAs

The two old risk assessments found for corn are attached.

Brenda May, Chief
Science Information Management Branch and
Information Management and Contract Support Branch (Acting)
Health Effects Division (Mail Code 7509P)
Office of Pesticide Programs US EPA
(703) 308-6175
may.brenda@epa.gov

From: Rowland, Jess
Sent: Tuesday, February 03, 2015 3:53 PM
To: May, Brenda
Subject: FW: HED RAs

Sent from my Windows Phone

From: Smith, Charles
Sent: 2/3/2015 11:44 AM
To: Knorr, Michele
Cc: Wakefield, Benjamin J.; Goerke, Ariadne; Rowland, Jess
Subject: RE: HED RAs

Ex. 5 Deliberative Process (DP)

Charles "Billy" Smith
Branch Chief RAB1
Health Effects Division
Office of Pesticide Programs
703-305-0291

From: Knorr, Michele
Sent: Tuesday, February 03, 2015 10:03 AM
To: Smith, Charles
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: RE: HED RAs

Ex. 5 Deliberative Process (DP)

Michele L. Knorr
Attorney
Pesticides and Toxics Law Office
Office of General Counsel
202-564-5631

From: Smith, Charles
Sent: Tuesday, February 03, 2015 9:31 AM
To: Knorr, Michele
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: RE: HED RAs

The 2003 document you reference was not a new registration but simply a label amendment. That is why there was no risk assessment and only a chemistry document. The original GM uses were registered in 96 (soybean) and 98 (corn).

Charles "Billy" Smith
Branch Chief RAB1
Health Effects Division
Office of Pesticide Programs
703-305-0291

From: Knorr, Michele
Sent: Tuesday, February 03, 2015 9:26 AM
To: Smith, Charles
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: RE: HED RAs

Ex. 5 Deliberative Process (DP)

Michele L. Knorr
Attorney
Pesticides and Toxics Law Office
Office of General Counsel
202-564-5631

From: Smith, Charles
Sent: Monday, February 02, 2015 7:50 AM
To: Knorr, Michele
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: RE: HED RAs

I will reiterate that the original GM uses were registered long ago....before we really even were doing specific quantitative RAs. I have added a 2002 assessment to the folder that included RoundUp Ready wheat. I don't see a 2003 assessment in our database. I still think focusing on the 2012 RA is the best as it reflects the current state of the science for glyphosate. It is what was "used" for Enlist.

The RED for glyphosate is available on line here:
http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf
However, this was from 1994 which was before the GM uses were even registered.

Charles "Billy" Smith
Branch Chief RAB1
Health Effects Division
Office of Pesticide Programs
703-305-0291

From: Knorr, Michele
Sent: Friday, January 30, 2015 4:20 PM
To: Smith, Charles
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: Re: HED RAs

We are still considering what is needed, but we really need to focus on the GM uses. There was a 2003 assessment for Monsanto over the top - can you look into this. Also do you have a copy of the TRED? Bob plans to send over a note that lays out this in more detail.

Michele Knorr
Pesticides and Toxic Substances Law Office
Office of General Counsel
U.S. EPA
202-564-5631

From: Smith, Charles
Sent: Friday, January 30, 2015 1:33 PM
To: Knorr, Michele
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: RE: HED RAs

The 2012 risk assessments include all uses of glyphosate including the GM corn and soybean which were registered some time ago. I believe soybeans started around 1996 and corn around 1998. This was truly the formative stage of what I would consider our "modern" risk assessments. On top of that, the only thing that would be unique to the GM uses would be some metabolism data and field trial data which are "included" in the 2012 residue chemistry and dietary assessments.

Charles "Billy" Smith
Branch Chief RAB1
Health Effects Division
Office of Pesticide Programs
703-305-0291

From: Knorr, Michele
Sent: Friday, January 30, 2015 1:24 PM
To: Smith, Charles
Cc: Wakefield, Benjamin J.; Goerke, Ariadne
Subject: HED RAs

Billy - do you know when the latest RA was done on GM corn and soybeans? Could we see those RAs? We may need those and the data cited, and then we would put in the RAs you just gave us as well - possibly. Just trying to see where we need to make a cut on this difficult record. Thanks for all your help and patience.

Michele Knorr
Pesticides and Toxic Substances Law Office
Office of General Counsel
U.S. EPA
202-564-5631

MEMORANDUM

DATE: 1/27/97

SUBJECT: Time-Limited Tolerances for Residues of
**Glyphosate in/on Field Corn, Sorghum, and Oat
Commodities.**

DP Barcode: D231386 Caswell No.: 661A
PC No.: 417300 PRAT Case #: 280708
Class: Herbicide
PP nos: 5F4555, 6E4645, 8F3672, 8F3673

TO: Philip Errico, Acting Manager, PM Team 25
Vickie Walters, Reviewer, PM Team 25
Registration Division (7505C)

FROM: Jim Carleton, George Kramer, Barbara Madden,
Catherine Eiden, Felicia Fort, Rich Griffin,
Linnea Hansen, Deborah McCall and Steve Robbins
Registration Team
Risk Characterization and Assessment Branch
Health Effects Division (7509C)

THROUGH: Michael S. Metzger, Acting Chief
Risk Characterization and Assessment Branch
Health Effects Division (7509C)

INTRODUCTION

Monsanto Co. is petitioning for time-limited tolerances for glyphosate in/on field corn grain, fodder, and aspirated grain fractions (PP#8F3673); grain sorghum and grain sorghum fodder (PP#8F3672); oats (PP#6E4645), and corn forage (PP#5F4555) from use of Roundup® Ultra Herbicide (524-475). The proposed tolerances for residues of glyphosate are:

Field corn grain, 1.0 ppm
Field corn forage, 1.0 ppm
Field corn fodder, 100 ppm
Aspirated grain fractions, 200 ppm

Sorghum grain, 15 ppm
Sorghum grain fodder, 40 ppm
Oat, 20 ppm

This petition is being examined with regard to the criteria set forth in the Food Quality Protection Act (FQPA). The Registrant has submitted no new toxicology or residue chemistry data with this petition, but did include a notice of finding that covers aggregate exposure and risk assessment for glyphosate based on proposed uses.

RECOMMENDATION

HED has evaluated the petitions for the establishment of time-limited tolerances for glyphosate on field corn, sorghum, and oat commodities. At this time, no additional concerns for exposure to infants and children were identified. Estimated aggregate chronic risk from combined dietary, non-dietary, and drinking water exposures for glyphosate does not exceed HED's level of concern.

Due to the absence of human health concerns as outlined above, HED can recommend in favor of granting a one year time-limited tolerance for residues of glyphosate on field corn, sorghum, and oat commodities.

RISK CHARACTERIZATION

Dietary Risk- Food: Chronic dietary exposure estimates for permanent and time-limited glyphosate tolerances resulted in a Theoretical Maximum Residue Contribution (TMRC) that is 3% of the reference dose. There are no concerns for acute dietary exposure at this time.

Non-occupational (Residential) Risks: Glyphosate is registered for use on non-food sites including lawns, ornamental plants, and hedgerows. However, available data indicated no evidence of significant toxicity via dermal or inhalation routes, therefore this risk assessment is not required.

Dietary Risk- Water: HED does not have available data to perform a complete quantitative risk assessment for the U.S. general population's exposure to glyphosate in drinking (ground and surface) water at this time (exposure estimates based upon limited available monitoring data are presented in Attachment II). Environmental fate data for glyphosate indicates little potential for the chemical to migrate to ground water, but some potential for residues to migrate to surface waters. Glyphosate is not highly mobile and not persistent in a soil and water

environment. HED will assume that drinking water risk is 10% of the total allowable chronic risk until further data are provided.

Aggregate Exposure/Risk: Based on the available data and assumptions used for dietary/water/residential exposure and risk estimates, the population groups estimated to be the most highly exposed to glyphosate are non-nursing infants <1 year old and children 1-6 years old, with a risk estimate from combined sources equalling 13% of the RfD for chronic risk.

Occupational Exposures: Data indicated no evidence of significant toxicity via the dermal or inhalation routes; therefore occupational and residential risk assessments are not required at this time.

CONCLUSIONS

Hazard Assessment for Glyphosate

1. Occupational Exposure Endpoint Selection for Glyphosate:
An Ad Hoc Toxicology Endpoint Selection Committee concluded this risk assessment is not required, based on the lack of any observable effects in a 21-day dermal toxicity study at the limit dose and the observation of no adverse effects in a developmental toxicity study in rats up to 1000 mg/kg/day and rabbits up to \geq 175 mg/kg/day. Therefore, worker exposure risks (MOEs) will not be calculated based on available data which indicates no evidence of significant toxicity by the dermal or inhalation routes.
2. Dietary Endpoint Selection
 - a) Acute Risk No endpoint was selected by an Ad Hoc TES Committee so this risk assessment was not required.
 - b) Chronic Risk. RfD = 2 mg/kg/day. On August 27, 1992, the Reference Dose Peer Review Committee recommended the RfD for glyphosate be established at 2 mg/kg/day. The RfD was based on the maternal toxicity NOEL of 175 mg/kg/day from the rabbit developmental toxicity study (MRID 00046363) using an uncertainty factor (UF) of 100. The LOEL of 350 mg/kg/day (highest dose tested) was based on treatment-related findings of diarrhea, nasal discharge, and death (62.5% of does died by gestation day 21). Developmental toxicity was not observed at any dose tested.
 - c) Cancer Risk. Glyphosate has been classified as a Group E chemical (evidence of non-carcinogenicity for humans) by the Cancer Peer Review Committee (6/26/91). The

classification was based on a lack of convincing evidence of carcinogenicity in adequate studies with two animal species, rat and mouse.

d) Infants and Children

i) Developmental Studies

Rat - In the rat developmental toxicity study (MRID # 00046362), the maternal (systemic) NOEL is 1000 mg/kg/day. The maternal (systemic) LOEL of 3500 mg/kg/day was based on the following treatment-related effects: diarrhea, decreased mean body weight gain, breathing rattles, inactivity, red matter around the nose and mouth, and on forelimbs and dorsal head, decreases in total implantations/dam and inviable fetuses/dam, and death (24% of the group). The developmental (pup) NOEL is 1000 mg/kg/day. The developmental (pup) LOEL of 3500 mg/kg/day was based on treatment-related developmental effects observed only in the high-dose group of: increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights.

Rabbit - In the rabbit developmental toxicity study (MRID # 00046363), the maternal (systemic) NOEL is 175 mg/kg/day. The maternal (systemic) LOEL of 350 mg/kg/day was based on treatment-related effects that included: diarrhea, nasal discharge, and death (62.5% of does died by gestation day 21). The developmental (pup) NOEL is \geq 175 mg/kg/day (insufficient litters were available at 350 mg/kg/day to assess developmental toxicity). Developmental toxicity was not observed at any dose tested.

ii) Reproduction Studies

Rat - A three-generation reproduction study was conducted with Sprague-Dawley rats (MRID # 00105995), the parental NOEL/LOEL is \geq 30 mg/kg/day (highest dose tested). The only effect observed was an increased incidence of focal tubular dilation of the kidney (both unilateral and bilateral combined) in the high-dose male F_{3b} pups.

Since the focal tubular dilation of the kidneys was not observed at the 1500 mg/kg/day level (HDT) in the 2-generation rat reproduction (see below), but was observed at the 30 mg/kg/day level (HDT) in the 3-generation rat reproduction study, the OPP Developmental Peer Review Committee concluded that the latter was a spurious rather than glyphosate-related

effect. Therefore, the parental and reproductive (pup) NOELs are ≥ 30 mg/kg/day.

Rat - A two-generation reproduction study was conducted with Sprague-Dawley rats (MRID # 41621501). Treatment-related effects observed in the high dose group included: soft stools, very frequent, in the F_0 and F_1 males and females, decreased food consumption and body weight gain of the F_0 and F_1 males and females during the growth (prematuring) period, and decreased body weight gain of the F_{1a} , F_{2a} and F_{2b} male and female pups during the second and third weeks of lactation. Focal tubular dilation of the kidneys, observed in the 3-generation study, was not observed at any dose level in this study. Based on the above findings, the parental and developmental (pup) NOEL's are 500 mg/kg/day and the parental and developmental (pup) LOEL's are 1500 mg/kg/day. The reproductive toxicity NOEL is ≥ 1500 mg/kg/day.

Occupational Exposures

Available data indicated no evidence of significant toxicity by the dermal or inhalation routes. Worker risk assessment is not required, therefore this exposure has not been assessed.

Some glyphosate end-use products (non-"homeowner" usage only) are in Toxicity Categories I and II for dermal and eye irritation, and have been associated with illnesses or injuries related to skin or eye irritation (J. Evans, OREB, 11/18/92). However, under the protective clothing requirements of the Worker Protection Standard (WPS), handlers of these products are expected to be adequately protected.

Aggregate Exposure (Dietary- Food, Dietary- Water & Residential)

Dietary Exposure-Food

The nature of the residue in plants and animals, enforcement methodology and residue chemistry data in support of these petitions were all previously evaluated by CBTS (PP#8F3673, PP#8F3672, PP#6E4645 and PP#5F4555).

1. The nature of the residue in plants and animals is adequately understood and consists of the parent, glyphosate. The HED Metabolism Committee has decided that only glyphosate parent is to be regulated in plant and animal commodities, and that the major metabolite, AMPA (aminomethyl phosphonic acid) is not of toxicological concern regardless of its level in food (see Metabolism Committee Memo, R. Perfetti 3/17/94).

2. Adequate enforcement methods are available for analysis of residues of glyphosate in or on plant commodities. These methods include GLC (Method I in *Pesticides Analytical Manual (PAM) II*; the limit of detection is 0.05 ppm) and HPLC with fluorometric detection. Use of the GLC method is being discouraged due to lengthiness of the procedure. The HPLC method has undergone successful Agency validation and was recommended for inclusion in *PAM II*; the limit of detection is 0.0005 ppm. A GC/MS method for glyphosate in crops has also been validated by ACL (Memo, G. Kramer, 3/21/95, PP#5F04555). This method has not yet been submitted for publication in *PAM-II*.
3. As a result of these uses, residues of glyphosate are not expected to exceed:
 - Corn, field, grain, 1.0 ppm
 - Corn, field, forage, 1.0 ppm
 - Corn, field, stover, 100 ppm
 - Aspirated grain fractions, 200 ppm
 - Sorghum, grain, grain, 15 ppm
 - Sorghum, grain, stover, 40 ppm
 - Oats, 20 ppm
4. Secondary residues in animal commodities are expected from this use. However, the established and proposed livestock tolerances are adequate to cover secondary residues which may result from feeding field corn and sorghum commodities with residues of glyphosate to animals. Since no U.S. registration has been proposed for oats, it has been concluded that oat feed items are not likely to enter channels of trade in the U.S.
6. Acute Dietary Risk. There is no acute dietary exposure endpoint of concern for glyphosate.
7. Chronic Dietary Risk. Chronic dietary exposure estimates (DRES) for glyphosate are summarized in Attachment III (B. Steinwand, 6/18/96). Published (permanent and time-limited) glyphosate tolerances result in a Theoretical Maximum Residue Contribution (TMRC) that is equivalent to the following percents of the RfD:

U.S Population	1%
Nursing Infants	1%
Non-Nursing Infants (<1 year old)	3%
Children (1-6 years old)	3%
Children (7-12 years old)	2%

The subgroups listed above are: (1) the U.S. population (48

states); (2) those for infants and children; and, (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

8. Cancer Risk. Glyphosate is classified as a Group E (non-carcinogen) chemical by the HED Cancer Peer Review Committee (10/30/91). Therefore, a quantitative cancer risk assessment is not required.
9. International Harmonization. Codex MRL's for the residues of glyphosate exist on corn and the straw and fodder, dry of cereal grains at 0.1 and 100 ppm respectively. Mexican limits on maize exist at 0.1 ppm. Canadian limits on all other food crops exist at 0.1 ppm. HED suggests the petitioner consider providing all relevant studies to Codex once the U.S. tolerances are established in order that the Codex MRLs may be amended to accommodate U.S. use needs.

Dietary Exposure and Risk Estimates- Water

HED does not have available data to perform a complete quantitative risk assessment for the U.S. general population's exposure to glyphosate in drinking (ground or surface) water at this time. Environmental fate data for glyphosate indicate little potential for the chemical to migrate to ground water, but some potential for residues to migrate to surface waters. Glyphosate is not highly mobile and not persistent in a soil and water environment. HED will **assume that drinking water risks are 10% of the total allowable chronic risk** until further data are provided. Based on analysis of water monitoring data for a large number of pesticides with varying toxicities, soil mobility characteristics, environmental fate profiles, the assumption of 10% of the total acute and chronic risk allocated to drinking water is considered conservative and protective of the public health. This exposure estimate is very conservative and will need refinement with time as more environmental fate and monitoring data on glyphosate becomes available.

Non-Occupational Exposure

Glyphosate is registered for uses on non-food sites such as turf that result in non-occupational exposures. However, since there are no toxicological endpoints for non-dietary exposures, the resulting risks cannot be assessed, therefore these exposures have not been estimated.

Total Aggregate Exposure (Dietary + Water + Residential)

- a) Chronic Risk: Based on the available data and assumptions used for dietary/water/residential exposure and risk estimates, the population group estimated to be the most highly exposed to glyphosate is non-nursing infants (<1 year old), with a risk estimate from combined sources equalling 13% of the RfD (dietary = 3% + drinking water = 10%).

Cumulative Effects

Glyphosate is structurally similar to other phosphono amino acids like glufosinate ammonium, fosamine ammonium, and sulfosate. Further, other pesticides may have common toxicity endpoints with glyphosate.

However, the Agency has not made a determination whether glyphosate and any other pesticide have a common mode of toxicity and require cumulative risk assessment. For the purposes of this tolerance and registration application, the Agency has considered only risks from glyphosate. If required, cumulative risks will be assessed as part of Reregistration and tolerance reassessment, and when methodologies for determining common mode of toxicity and for performing cumulative risk assessment are finalized.

Determination of Safety for Infants and Children

The toxicological database for evaluating pre- and post-natal toxicity for glyphosate is considered to be complete at this time. In the rabbit, no developmental toxicity was observed at doses where significant maternal toxicity was noted (death and clinical signs at 350 mg/kg/day, highest dose tested). In the rat developmental toxicity study, maternal (systemic) toxicity was noted at 3500 mg/kg/day dose level (HDT) as diarrhea, decreased mean body weight gain, breathing rattles, inactivity, red matter around the nose and mouth, and on forelimbs and dorsal head, decreases in total implantations/dam and inviable fetuses/dam, and death (24% of the group). The developmental (pup) NOEL is 1000 mg/kg/day. The developmental (pup) toxicity was exhibited only in the high dose as increased number of litters and fetuses with unossified sternebrae, and decreased mean fetal body weights. However, these developmental effects were assumed to be due to the extreme maternal toxicity. No effects on reproductive parameters were observed.

In the rat 2-generation reproduction study, parental toxicity was observed at 1500 mg/kg/day as soft stools, decreased food consumption and body weight gain. The developmental (pup) toxicity was also only exhibited at 1500 mg/kg/day as decreased body weight gain of the F_{1a} , F_{2a} and F_{2b} male and female pups during the second and third weeks of lactation.

Based on the available toxicity data, HED does not have concerns regarding special sensitivities for infants and children exposed to residues of glyphosate in the diet and concludes that establishment of these time-limited tolerances should not pose an unacceptable risk to infants and children. Thus, the addition of an additional uncertainty factor will not be required.

ATTACHMENTS

- I. Magnitude of the Residue - Crop Field Trials
- II. Exposure and Risk Estimates from Water
- III. DRES analysis for glyphosate

cc: PP#8F3673, J. Carleton (HED/OREB), G. Kramer (HED/CBTS)
RDI: Team (1/23/97), M.S. Metzger (1/27/97)

Attachment I: Magnitude of the Residue - Crop Field Trials

Magnitude of the Residue - Crop Field Trials

The following summary of residue field trial data are reproduced from previous CBTS reviews as noted below. No new residue data were presented with this revised petition.

Corn grain and fodder (W. Cutchin, 3/21/96, PP#8F03673, D216229 and D216230, CBTS No. 15700, and 15701)

The results of twelve corn residue studies were submitted. Eleven studies were conducted in Region V - Michigan, Iowa, Missouri, Illinois, Wisconsin, Indiana, Ohio, Kentucky, Minnesota, Nebraska, and South Dakota and one study in Region VI-Texas.

For each of the residue studies, there was a control plot and treated plot. Roundup® Herbicide was applied to the treated plot to mature corn plants by ground equipment at the maximum rate of 3 qt (2.25 lb ai)/A. Grain and fodder were harvested six to eight days after application. The results of the analysis indicate that residues of glyphosate on corn grain ranged from ND to 0.54 ppm averaging 0.08 ppm. The corn fodder samples had 3.7 to 92 ppm glyphosate residues averaging 35 ppm.

Processing Studies

Samples of field corn from the Iowa and Illinois studies were milled to produce corn processed commodities. The highest concentration factor was 672 on grain screenings from Illinois. The requested tolerance for aspirated grain fractions is based on the highest average field trial (HAFT) grain residue found, 0.54 ppm, multiplied by the highest concentration factor found on grain dust, 395. A tolerance on milled byproducts would be calculated from the highest average grain residue, 0.54 ppm, multiplied by the average concentration factor found on dry milled commodities, 1.12 $((1.71 + 0.52)/2)$, found on flour. The result of this calculation, 0.6 ppm $(0.54 \text{ ppm} * 1.12)$, is lower than the requested tolerance on the corn grain, therefore no tolerance is required for milled byproducts.

Corn Forage (G. Kramer, PP#5F04555, 3/14/96, D217539 and D217541, CBTS No. 15913 and 15914)

A total of 22 field residue trials were conducted in 1994 in 16 different states, which together accounted for 92% of the U.S. grain corn acreage in 1992 (*Agricultural Statistics*, 1993). Three different treatment regimens were employed in separate plots at each site. The spray volume was 11-22 gal/A. The interval between the early and late postemergence applications

ranged from 13-38 days. Forage samples were harvested from each treated plot 25-98 days after the final postemergence application. Fodder and grain samples were harvested from each treated plot 76-153 days after the final postemergence application or 6-8 days after the preharvest application. Samples were analyzed for glyphosate and AMPA using the HPLC-fluorometric method previously reviewed by CBTS (Memo, R. Cook 1/29/91). Analysis of the treated samples showed that the maximum glyphosate residue in corn forage was 0.82 ppm, in corn fodder was 41.2 ppm, and in corn grain was 0.36 ppm.

Sorghum (S. Willett, 4/17/96, PP#8F03672, D207119 and D207121, CBTS No. 14303 and 14304)

Roundup^R herbicide (41% ai) was applied using ground equipment as a single preharvest treatment at eight locations in Arkansas (1), Kansas (2), Missouri (1), Nebraska (1) Oklahoma (1), South Dakota (1), and Texas (1) in 1992. The application rates were 0.74 (Texas only) to 0.75 (0.5X) lb ai acid equivalents/acre, and 1.48 (Texas only) to 1.50 (1X) lb ae/acre, and the spray volume ranged from 10 to 20 gal/acre. Six to eight days after application of glyphosate, grain and fodder samples were harvested from control, 0.5 X, and 1X plots, and stored frozen until analyzed. Results showed that residues ranged from 1.4 to 13.5 ppm in sorghum grain, 2.9 to 33.1 ppm in sorghum fodder, and 3.1 to 37.0 ppm in sorghum hay.

Oats (S. Willett, 5/8/96, PP#6E4645, D223639, CBTS No. 16948)

Monsanto submitted residue data from trials conducted from 1993 to 1994 in Canada (MRID Nos. 43927401, 43927402), and from 1978 to 1986 in Europe (43870201, 43870202 and 43870203). All of the data have been previously reviewed by the Pest Management Regulatory Agency of Canada in support of Canadian or Codex MRL's and determined to be acceptable. Table 1 summarizes the residue data as reviewed by PMRA.¹

¹EPA/OPP and the Pest Management Regulatory Agency of Canada (PMRA) recently announced that it would share pesticide data reviews. See EPA Press Advisory dated Monday April 22, 1996.

TABLE 2. SUMMARY OF GLYPHOSATE RESIDUES IN OATS (INTERNATIONAL TRIALS)

Country	Rate (kg ae/ha)	# of Sites	PHI (days)	Glyphosate Residues (ppm)	Median Glyphosate (ppm)
Canada	0.9	7	7-14	0.9-6.2	3.6
Canada ²	1.8 (2X)	1		13-16	15
Norway	1.0	4	7-15	1.0-3.1	2.2
Finland	1.08	4	7-14	2.8-13	10
Europe ³	1.44	20	5-15	1.0-10	4.7
Germany	1.8	7	5-14	4.3-17	8.3

CBTS concludes that the residue data adequately support the requested tolerance of 20 ppm for residues of glyphosate on imported oats.⁴ Additional residue data may be required in the event that a U.S. registration for use of glyphosate on oats is sought.

Processing Study Data

Oats may be processed to produce flour and groats/rolled oats. Therefore the petitioner has submitted processing study data.

Oat grain from a field trial conducted in 1981 in the U.K. (MRID No. 43870204) was processed to groats and hulls. Glyphosate residue levels in oat grain from 0.5X, 1X and 2X the European label rate [4L Roundup (1.44 kg ae)/ha] and harvested 7 days after treatment ranged from 0.8 to 11.3 ppm. Analyses of the corresponding groat samples indicated no concentration as a result of processing. Residues concentrated an average of 2.6X in oat hulls. However oat hulls are not considered to be a separate human food or animal feed item (see Residue Chemistry Guidelines, Table I, OPPTS 860.1000), and so no tolerance is needed for oat hulls. Glyphosate residue levels were not reported for oat flour in this study. However, the petitioner has referenced a wheat milling study to be used as a surrogate which has been previously reviewed by CBTS. That study indicates that glyphosate residues do not concentrate as a result of processing to flour (see 1/29/91 memo of R. Cook, PP No. 0F3865).

Monsanto has not requested import tolerances for oat forage, oat

²These residue data were generated at a site in Oakville Manitoba. The plot was shorter and wider than the other sites, and required two passes with the sprayer. This possibly resulted in considerable overlap resulting in a 2X rate and higher residue values. The Canadian MRL is 10 ppm (see attachment 1).

³See also PP No. 2E4118, MRID No. 43827802.

⁴Draft internal guidance on data requirements for import tolerances suggests that data review of pesticides with existing U.S. tolerances and adequate toxicity studies should be minimal, and that CODEX tolerances should be adopted if possible. See 11/95 CBTS working paper.

hay or oat straw since these commodities are used typically as on-farm animal feed items, and it is extremely unlikely that these commodities would enter channels of trade in the U.S..

CBTS concurs with Monsanto's position that tolerances are not needed for oat forage, oat hay or oat straw.

Meat, Milk, Poultry, and Eggs (W. Cutchin, 3/21/96, PP#8F03673, D216229 and D216230, CBTS No. 15700, and 15701)

Feeding studies have been conducted in which cattle, swine, and poultry were dosed with a (9:1) mixture of glyphosate and AMPA at 0, 40, 120, and 400 ppm for 28 days and then slaughtered. No residues were found in milk or fat at any dosing level. Only minimal residues were found in eggs and muscle at 400 ppm. Significant residue levels were found in animal liver and kidney at the 120 and 400 ppm levels (PP#6F3380/ FAP6H5502, DEB#s: 4285 and 4286, 1/30/89).

Based on the above feeding study, secondary residues from these new uses are not expected to exceed currently established animal tolerances.

Attachment II: Exposure and Risk Estimates From Water**CONCLUSIONS**

Glyphosate residues can migrate to ground water and surface water as evinced from the monitoring study data available to date and presented here. However, based on the available monitoring data for drinking water sources monitored for glyphosate residues, HED does not, at this time, have a concern regarding the impacts of glyphosate residues on drinking water with respect to human health. Even at the maximum level detected in ground water reported here, glyphosate residues do not pose a human health hazard. This maximum concentration used to calculate risk is not considered typical or representative of residues of glyphosate in drinking water. Data are unavailable to assess the environmental fate (persistence and mobility) of glyphosate's main degradate (AMPA).

USE PATTERN

Glyphosate is a nonselective herbicide used in the control of perennial, deep-rooted grasses and broadleaf weeds, as well as woody brush on a wide variety of crops and non-crop areas. This use pattern may impact ground water and surface water, and ultimately drinking water. Therefore, an assessment of the risks posed to human health from the potential impact of the use of glyphosate on drinking water is required. Data are available to assess the environmental fate of glyphosate. Glufosinate, fosamine, and sulfosate are pesticides structurally related to glyphosate.

1. Exposure Estimates: Ground Water

HED has estimated the exposure and risk associated with the highest glyphosate residues detected in ground water. These calculations indicate that even at high concentrations in ground water, glyphosate residues do not pose a human health hazard.

For the purposes of these exposure estimates, a few assumptions have been made and are given below:

Water consumption is defined as all water obtained from the household tap that is consumed either directly as a beverage or used to prepare foods (such as mixing water with a can of soup) and beverages (such as diluting frozen juice concentrate). For the adult exposure calculation, the average adult body weight is assumed to be 70 kg, and it is assumed that the average adult consumes 2 liters of water (L)/day. For the children's exposure, the average body weight is assumed to be 10 kg and the average water consumption is assumed to be 1 liter per day.

The other assumption inherent in this calculation is that water from the same source containing the same contaminant level (the maximum monitored concentration available from the sources cited) is consumed throughout a 70-year lifetime. The second of these assumptions is extremely conservative, since most members of the U.S. population move at some time during their lifetime and do not live in the same area or drink from the same water source for a 70-year lifetime.

Exposure is calculated using the following formula for adults:

Exposure = (chemical concentration in ug/L in consumed water) * (10^{-3} mg/ug) ÷ (70 kg body weight) * (2 L water consumed/day)

For children, the exposure is calculated using the following formula:

Exposure = (chemical concentration in ug/L in consumed water) * (10^{-3} mg/ug) ÷ (10 kg body weight) * (1 L water consumed/day)

Adult Exposure

Glyphosate Exposure (drinking water wells @ maximum concentration detected) = (150 ug/L) * (10^{-3} mg/ug) ÷ (70 kg body weight) * (2L/day) = 4.3×10^{-3} mg/kg/day.

Children's Exposure

Glyphosate Exposure (drinking water wells @ maximum concentration detected) = (150 ug/L) * (10^{-3} mg/ug) ÷ (10 kg body weight) * (1L/day) = 1.5×10^{-2} mg/kg/day.

2. Estimated Risk: Ground Water

HED calculates a percentage of the RfD to estimate the risk for drinking water using the following formula:

%RfD = Exposure (mg/kg/day) ÷ RfD (mg/kg/day) x 100

The chronic dietary risk is calculated using the RfD of 2 mg/kg/day, established from the rabbit developmental study.

Adult %RfD (drinking water wells @ maximum concentration detected) = (4.3×10^{-3} mg/kg/day ÷ 2) x 100 = 0.215 %RfD

Children's %RfD (drinking water wells @ maximum concentration detected) = (1.5×10^{-2} mg/kg/day ÷ 2) x 100 = 0.75 %RfD

1. Environmental Fate Profile

The EFGWB One-Liner database was searched for information on the environmental fate of glyphosate. The HED Metabolism Committee has determined that the residue of concern for glyphosate is the parent molecule. An environmental fate profile for glyphosate is given below:

Glyphosate

Solubility: 1.2×10^4 ppm @ 20°C

Hydrolysis: stable (pH = 3)

stable (pH = 6)

stable (pH = 9)

Photolysis (water) $t_{1/2}$: stable (pHs = 5, 7, 9)

Photolysis (soil) $t_{1/2}$: 90 days

Soil $t_{1/2}$ (aerobic): < 1-3 days

Aquatic $t_{1/2}$ (aerobic): 7 days

Aquatic (anaerobic) $t_{1/2}$: 1-7 weeks

Mobility: K_d = 22-90 ml/gm (slightly mobile in soils)

Field dissipation $t_{1/2}$: range 1-several months

Aquatic dissipation: residues of glyphosate decreased rapidly from water, but persisted in pond sediments.

2. Monitoring Data: Ground Water and Surface Water

The "Pesticides in Ground Water Database" was searched for monitoring data on glyphosate residues in ground water. Information on residues of glyphosate in surface waters were not readily available within HED for this review and have not been included in this assessment.

Ground water monitoring wells (representative of drinking water) were sampled in CA (116 wells sampled from 1984-1988), MO (40 wells sampled in 1986), TX (31 wells sampled in 1988), and VA (60 wells sampled in 1987). All samples from the CA and MO wells had non-detectable residues. One sample from the TX well samples contained 150 ppb glyphosate residues, and 6 samples from the VA wells had detectable residues of glyphosate ranging from 0.004 to 0.009 ppb.

HEALTH CRITERIA

The lifetime health advisory, MCL and MCLG for glyphosate are the same and given as 700 ppb in the U.S. EPA Office of Drinking Water's "Drinking Water Health Advisory: Pesticides".

AGGREGATE RISK

For the purposes of calculating the aggregate risk from glyphosate uses, the potential risk estimated for residues of

glyphosate in drinking water as a percentage of RfD are given below:

% RfD is calculated as Exposure Estimate in Water (mg/kg/day) ÷ RfD (mg/kg/day) x 100.

The percentage of RfD is calculated for the exposure estimate for glyphosate residues in ground water for adults and children. The RfD for glyphosate is 2 mg/kg/day.

$$\% \text{ RfD (Adults)} = 4.3 \times 10^{-3} \text{ mg/kg/day} \div 2 \text{ mg/kg/day} \times 100 = <1\%$$

$$\% \text{ RfD (Children)} = 1.5 \times 10^{-2} \text{ mg/kg/day} \div 2 \text{ mg/kg/day} \times 100 = <1\%$$